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10/622,076	07/17/2003	**Rudolf Gilmanshin**	C0989.70054US00	1842

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/622,076	GILMANSHIN, RUDOLF	
	Examiner	Art Unit	
	ANGELA BERTAGNA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-7,9,11-17,19-34,68,91,125,126 and 128-130* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-7,9,11-17,19-34,68,91,125,126 and 128-130* is/are rejected.

7)☒ Claim(s) *11 and 12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/16/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 4, 2008 has been entered.

Claims 1, 2, 5-7, 9, 11-17, 19-34, 68, 91, 125, 126, and 128-130 are currently pending and are the subject of this Office Action.

Information Disclosure Statement

2. Applicant's submission of an Information Disclosure Statement on January 16, 2009 is acknowledged. A signed copy is enclosed.

Claim Objections

3. Claims 11 and 12 are objected to for the following informalities: Replacing the words "the enzyme" in line 1 of claims 11 and 12 with "the nucleic acid binding enzyme" is suggested to improve consistency with claim 1.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1, 2, 5-7, 11, 13-16, 24-26, 31, 91, 126, 128, and 129 are rejected under 35 U.S.C. 102(b) as being anticipated by Cheng et al. (Biochemical and Biophysical Research Communications (1991) 174(2): 785-789; cited previously).

These claims are drawn to a method for analyzing a nucleic acid polymer. The method comprises providing a conjugate comprising a nucleic acid binding enzyme and a nucleic acid tag molecule, contacting the nucleic acid polymer with the conjugate, and determining a pattern of binding of the conjugate to the polymer that is not based on the catalytic activity of the enzyme. The nucleic acid binding enzyme binds non-specifically to the nucleic acid polymer, and the nucleic acid tag molecule binds specifically to the nucleic acid polymer. Also, the nucleic acid binding enzyme and the nucleic acid tag molecule are covalently linked.

Cheng analyzed the binding between HIV-1 reverse transcriptase and a primed nucleic acid template using UV cross-linking (see abstract and pages 786-787).

Regarding claims 1, 2, 91, 126, 128, and 129, Cheng teaches a method for analyzing a nucleic acid polymer (see page 786, last paragraph – page 787, first paragraph). Here, Cheng teaches combining a nucleic acid polymer (rA_{12-18}) with a nucleic acid tag molecule (dT_{10}) and a nucleic acid binding enzyme (HIV-1 reverse transcriptase) and performing UV cross-linking.

This step results in "providing a conjugate comprising a nucleic acid binding enzyme and a nucleic acid tag molecule" and "contacting the conjugate with a nucleic acid polymer". The UV cross-linking step simultaneously provides a covalently bound conjugate comprising the nucleic acid tag molecule and the nucleic acid binding enzyme that contacts the nucleic acid polymer. When the reactants are combined in solution (page 786, last paragraph), the HIV-1 RT inherently binds non-specifically to and translocates along the nucleic acid polymer. Since the nucleic acid tag molecule (dT_{10}) is complementary to the nucleic acid polymer ($rA_{12\text{-}18}$), it binds in a sequence-specific manner to label the nucleic acid polymer. In the method of Cheng, the reverse transcriptase enzyme does not cleave the nucleic acid polymer. The analysis of the cross-linked complexes by electrophoresis (Figures 1 & 2) constitutes determining a binding pattern of the conjugate to the nucleic acid polymer. This determination is based on the detection of radioactive labels present on the nucleic acid polymer and the nucleic acid binding enzyme, and therefore, is not dependent on the catalytic activity of HIV-1 RT (see pages 786-787 and Figures 1-2). Finally, the HIV-1 RT taught by Cheng is a nuclease since it inherently possesses RNase H activity (page 785, 1st paragraph). Therefore, Cheng anticipates the methods of claims 1, 2, 91, 126, 128, and 129.

Regarding claims 5-7 and 11, Cheng teaches that the nucleic acid polymer is RNA, the nucleic acid tag molecule is a DNA, and the enzyme is a DNA polymerase (page 786, last paragraph). Also, the nucleic acid tag molecule taught by Cheng is 10 nucleotides in length (page 786, last paragraph), which is within the claimed length range of 5-50 nucleotides.

Regarding claim 13, the nucleic acid tag molecule of Cheng (dT_{10}) is labeled with a detectable moiety, since it inherently can be detected indirectly via its ability to bind a labeled complementary oligonucleotide.

Regarding claims 14, 16, and 31, Cheng teaches that the nucleic acid binding enzyme and the nucleic acid polymer are labeled with detectable moieties, specifically radioactive labels (page 786, last paragraph). Cheng also teaches indirect detection of the nucleic acid binding enzyme by measuring the signal from the polymer in combination with the signal from a radiolabeled nucleotide substrate (dTTP) bound to the enzyme (pages 786-788 and Figures 1-2).

Regarding claim 15, the nucleic acid tag molecule of Cheng (dT_{10}) is labeled with a first detectable moiety, since it inherently can be detected indirectly via its ability to bind a labeled complementary oligonucleotide. Also, the nucleic acid binding enzyme of Cheng is labeled with a second detectable moiety, specifically a radioactive label (page 786, last paragraph).

Regarding claims 24-26, the nucleic acid polymer taught by Cheng is neither an *in vitro* amplified nucleic acid nor an antisense molecule (page 786). Also, the nucleic acid molecule taught by Cheng (dT_{10}) does not hybridize to bacterial or viral-specific sequences.

6. Claim 125 is rejected under 35 U.S.C. 102(b) as being anticipated by Fisher et al. (WO 98/19168 A1; newly cited) as evidenced by Chaudhry et al. (Nucleic Acids Research (1995) 23(19): 3805-3809; cited previously).

Claim 125 is drawn to a method for analyzing a nucleic acid polymer. The method comprises contacting the nucleic acid polymer with a conjugate comprising a nucleic acid tag molecule covalently linked to a DNA repair enzyme, a helicase, or a ligase. The nucleic acid

binding enzyme binds non-specifically to the nucleic acid polymer, and the nucleic acid tag molecule binds specifically to the nucleic acid polymer. A pattern of the binding between the conjugate and the nucleic acid polymer is then determined.

Fisher teaches a method for analyzing a nucleic acid polymer (such as DNA or RNA) using a conjugate consisting of a covalently linked oligonucleotide and nuclease P1 (see abstract and page 9, line 15 – page 10, line 14). The nucleic acid tag oligonucleotide hybridizes specifically to the nucleic acid target (page 13, lines 3-13). The nucleic acid binding enzyme (nuclease P1) inherently binds non-specifically to the nucleic acid polymer at least transiently, since it is conjugated to a short oligonucleotide that specifically binds to the nucleic acid polymer. After specific hybridization of the oligonucleotide tag molecule to the nucleic acid polymer, the hybridization pattern was detected (page 10, lines 3-14). Finally, as evidenced by Chaudhry et al., the S1 and P1 nucleases used in the conjugates of Fisher are DNA repair enzymes (see pages 3806-3808 and Figures 1-4 of Chaudhry).

7. Claims 1, 2, 5, 6, 9, 11-16, 24-27, 31, 91, 125, 126, 128, and 130 are rejected under 35 U.S.C. 102(e) as being anticipated by Taira et al. (US 2003/0199471 A1; newly cited).

These claims are drawn to a method for analyzing a nucleic acid polymer. The method comprises contacting the nucleic acid polymer with a conjugate comprising a nucleic acid binding enzyme and a nucleic acid tag molecule that are covalently linked to each another. The nucleic acid binding enzyme binds non-specifically to the nucleic acid polymer, and the nucleic acid tag molecule binds specifically to the nucleic acid polymer. A pattern of the binding between the conjugate and the nucleic acid polymer is then determined using a backbone-

specific label on the nucleic acid polymer. This determination is not based on the catalytic activity of the nucleic acid binding enzyme.

Regarding claims 1, 2, 12, 91, 125, 126, 128, and 130, Taira teaches a method for analyzing a nucleic acid polymer comprising: a first step of providing a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme that are covalently linked to each other and a second step of contacting the nucleic acid polymer with the conjugate (see, for example, paragraphs 82, 85, & 86; see also paragraphs 31, 33, & 36), wherein the nucleic acid binding enzyme binds to the nucleic acid polymer non-specifically and translocates along the nucleic acid polymer (see paragraphs 33, 36-38, 82, 85, 86, and 128), and wherein the nucleic acid tag molecule to bind to the nucleic acid polymer in a sequence-specific manner, thereby labeling the nucleic acid polymer (see paragraphs 31, 36-38, 85, 86, 106, and 128), and a third step of determining a pattern of binding of the conjugate to the nucleic acid polymer (paragraphs 36-38, 85, 86, and 106). In the method of Taira, the nucleic acid binding enzyme (helicase) does not cleave or modify the nucleic acid polymer, nor is the helicase detected based on its catalytic activity.

Regarding claims 5, 6, and 11, Taira teaches that the nucleic acid polymer is RNA, the nucleic acid tag molecule is RNA, and the nucleic acid binding enzyme is a helicase (paragraphs 43, 82, and 128). Taira further teaches that the nucleic acid polymer and the nucleic acid tag molecule may be DNA at paragraph 23. Taira also teaches that the nucleic acid binding enzyme may be a DNA polymerase or an RNA polymerase at paragraph 22.

Regarding claim 9, Taira teaches that the nucleic acid tag molecule and the nucleic acid binding enzyme are conjugated using a linker molecule (paragraph 82).

Regarding claims 13-16, Taira teaches that the nucleic acid tag molecule and the nucleic acid binding enzyme are labeled with a detectable moiety (see paragraphs 82 and 128, where the CTE region is a detectable moiety that labels both the nucleic acid tag molecule and the nucleic acid binding enzyme). Also, since the nucleic acid binding enzyme inherently contains epitopes that may be bound by detectably labeled antibodies, the nucleic acid binding enzyme is also labeled with a second detectable moiety, while the nucleic acid tag molecule is labeled with a first detectable moiety. The nucleic acid polymer (mRNA) of Taira is also labeled with a detectable moiety, since it inherently can be detected indirectly via hybridization of a labeled complementary nucleic acid probe.

Regarding claim 24, the mRNA target taught by Taira at paragraph 128 is not an *in vitro* amplified molecule.

Regarding claim 25, the ribozyme nucleic acid tag molecule taught by Taira at paragraph 128 is not an antisense molecule.

Regarding claim 26, Taira teaches ribozymes (nucleic acid tag molecules) that specifically bind to eukaryotic sequences (paragraph 64, for example).

Regarding claim 27, Taira teaches that the nucleic acid tag molecule is labeled with an agent, specifically the CTE region (paragraphs 82 and 128).

Regarding claim 31, Taira teaches detection of the ribozyme cleavage products, which results in indirect detection of the nucleic acid binding enzyme (paragraph 66).

8. Claims 1, 2, 5, 6, 9, 11-16, 24-27, 31, 91, 125, 126, 128, and 130 are rejected under 35 U.S.C. 102(a) as being anticipated by Tahira et al. (JP 2001/190282 A; newly cited).

It is noted Taira et al. (US 2003/0199471 A1) is an English language equivalent of the above Japanese language document. The citations below refer to the English language document.

These claims are drawn to a method for analyzing a nucleic acid polymer. The method comprises contacting the nucleic acid polymer with a conjugate comprising a nucleic acid binding enzyme and a nucleic acid tag molecule that are covalently linked to each another. The nucleic acid binding enzyme binds non-specifically to the nucleic acid polymer, and the nucleic acid tag molecule binds specifically to the nucleic acid polymer. A pattern of the binding between the conjugate and the nucleic acid polymer is then determined using a backbone-specific label on the nucleic acid polymer. This determination is not based on the catalytic activity of the nucleic acid binding enzyme.

Regarding claims 1, 2, 12, 91, 125, 126, 128, and 130, Taira teaches a method for analyzing a nucleic acid polymer comprising: a first step of providing a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme that are covalently linked to each other and a second step of contacting the nucleic acid polymer with the conjugate (see, for example, paragraphs 82, 85, & 86; see also paragraphs 31, 33, & 36), wherein the nucleic acid binding enzyme binds to the nucleic acid polymer non-specifically and translocates along the polymer (see paragraphs 33, 36-38, 82, 85, 86, and 128), and wherein the nucleic acid tag molecule to bind to the nucleic acid polymer in a sequence-specific manner, thereby labeling the nucleic acid polymer (see paragraphs 31, 36-38, 85, 86, 106, and 128), and a third step of

determining a pattern of binding of the conjugate to the nucleic acid polymer (paragraphs 36-38, 85, 86, and 106). In the method of Taira, the nucleic acid binding enzyme (helicase) does not cleave or modify the nucleic acid polymer, nor is the helicase detected based on its catalytic activity.

Regarding claims 5, 6, and 11, Taira teaches that the nucleic acid polymer is RNA, the nucleic acid tag molecule is RNA, and the nucleic acid binding enzyme is a helicase (paragraphs 43, 82, and 128). Taira further teaches that the nucleic acid polymer and the nucleic acid tag molecule may be DNA at paragraph 23. Taira also teaches that the nucleic acid binding enzyme may be a DNA polymerase or an RNA polymerase at paragraph 22.

Regarding claim 9, Taira teaches that the nucleic acid tag molecule and the nucleic acid binding enzyme are conjugated using a linker molecule (paragraph 82).

Regarding claims 13-16, Taira teaches that the nucleic acid tag molecule and the nucleic acid binding enzyme are labeled with a detectable moiety (see paragraphs 82 and 128, where the CTE region is a detectable moiety that labels both the nucleic acid tag molecule and the nucleic acid binding enzyme). Also, since the nucleic acid binding enzyme inherently contains epitopes that may be bound by detectably labeled antibodies, the nucleic acid binding enzyme is also labeled with a second detectable moiety, while the nucleic acid tag molecule is labeled with a first detectable moiety. The nucleic acid polymer (mRNA) of Taira is also labeled with a detectable moiety, since it can be detected indirectly via hybridization of a labeled complementary nucleic acid probe.

Regarding claim 24, the mRNA target taught by Taira at paragraph 128 is not an *in vitro* amplified molecule.

Regarding claim 25, the ribozyme nucleic acid tag molecule taught by Taira at paragraph 128 is not an antisense molecule.

Regarding claim 26, Taira teaches ribozymes (nucleic acid tag molecules) that specifically bind to eukaryotic sequences (paragraph 64, for example).

Regarding claim 27, Taira teaches that the nucleic acid tag molecule is labeled with an agent, specifically the CTE region (paragraphs 82 and 128).

Regarding claim 31, Taira teaches detection of the ribozyme cleavage products, which results in indirect detection of the nucleic acid binding enzyme (paragraph 66).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 17, 22, 23, and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taira et al. (US 2003/0199471 A1; newly cited) in view of Daskis et al. (WO 2001/46467 A2; newly cited) and further in view of Thompson et al. (US 6,348,317 B1; cited previously).

Claim 17 is drawn to the method of claim 16, wherein the nucleic acid polymer is labeled with a backbone-specific label. Claims 22 and 23 are drawn to the method of claim 13, wherein the nucleic acid tag molecule is labeled with a fluorescent molecule that is detected with a

fluorescence detection system. Claims 28-30 are drawn to the method of claim 27, wherein the agent is a photocleaving agent.

Taira teaches the methods of claims 1, 2, 5, 6, 9, 11-16, 24-27, 31, 91, 125, 126, 128, and 130, as discussed above.

Taira does not teach that the nucleic acid polymer is labeled with a backbone-specific label as required by claim 17. Taira also does not teach labeling the nucleic acid tag molecule with a fluorescent molecule as required by claims 22 and 23. Taira also does not that the nucleic acid tag molecule is labeled with a photocleaving agent as required by claims 28-30.

Daskis teaches a fluorescence-based method for detecting nucleic acid hybridization (see abstract and page 4, lines 4-25). Regarding claims 17, 22, and 23, Daskis teaches detecting a target nucleic acid by hybridizing a nucleic acid probe to the target nucleic acid in the presence of a fluorescent intercalating agent (*i.e.* a backbone-specific label) (see abstract and page 4, lines 4-25). Daskis also teaches that the fluorescent intercalating agent may be bound to the nucleic acid probe covalently or non-covalently (page 8, lines 16-24). Daskis teaches that the disclosed method permits rapid, sensitive, environmentally friendly, safe, and homogeneous monitoring of hybridization reactions (page 5, lines 1-7 and page 6, lines 7-25)

Regarding claims 28-30, as evidenced by Thompson, Daskis teaches fluorescent intercalating agents that are photocleaving agents (see page 8, lines 25-30 of Daskis and column 4, lines 3-25 and column 6, lines 1-31 of Thompson).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to combine the teachings of Taira and Daskis. An ordinary artisan would have been motivated to label the nucleic acid tag molecule (*i.e.* the ribozyme) and the mRNA target

molecule of Taira using the backbone-specific fluorescent intercalating agents taught by Daskis. An ordinary artisan would have been motivated to do so in order to obtain a rapid, sensitive, environmentally friendly, safe, and homogeneous method for analyzing the binding between the ribozyme-helicase conjugates of Taira and their mRNA targets. Thus, the methods of claims 17, 22, 23, and 28-30 are *prima facie* obvious over Taira in view of Daskis.

11. Claims 19, 20, 22, 23, 33, 34, and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taira et al. (US 2003/0199471 A1; newly cited) in view of Tegenfeldt et al. (WO 00/09757; cited previously).

Claims 19, 20, 33, and 34 are drawn to the method of claim 1, wherein a single molecule linear polymer analysis system is used to determine a pattern of binding of the enzyme-nucleic acid conjugate to the nucleic acid polymer. Claims 22 and 23 are drawn to the method of claim 13, wherein the nucleic acid tag molecule is labeled with a fluorescent molecule that is detected with a fluorescence detection system. Claim 68 is drawn to a method for analyzing a nucleic acid polymer comprising binding a covalently-linked conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme to a nucleic acid polymer and analyzing the binding using a linear polymer analysis system.

Taira teaches the methods of claims 1, 2, 5, 6, 9, 11-16, 24-27, 31, 91, 125, 126, 128, and 130, as discussed above.

Regarding claim 68, Taira teaches a method for analyzing a nucleic acid polymer comprising: a first step of providing a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme that are covalently linked to each other and a second step of

contacting the nucleic acid polymer with the conjugate (see, for example, paragraphs 82, 85, & 86; see also paragraphs 31, 33, & 36), wherein the nucleic acid binding enzyme binds to the nucleic acid polymer non-specifically and translocates along the polymer (see paragraphs 33, 36-38, 82, 85, 86, and 128), and wherein the nucleic acid tag molecule to bind to the nucleic acid polymer in a sequence-specific manner, thereby labeling the nucleic acid polymer (see paragraphs 31, 36-38, 85, 86, 106, and 128), and a third step of determining a pattern of binding of the conjugate to the nucleic acid polymer (paragraphs 36-38, 85, 86, and 106). In the method of Taira, the nucleic acid binding enzyme (helicase) does not cleave or modify the nucleic acid polymer, nor is the helicase detected based on its catalytic activity.

Taira does not teach the use of a single molecule linear polymer analysis system to analyze the binding of the helicase-ribozyme conjugate to the nucleic acid polymer.

Tegenfeldt teaches a linear polymer analysis system for optically analyzing polymers. Tegenfeldt teaches that the system is useful for performing a sequencing application wherein a nucleic acid is labeled with a fluorescent or radioactive label and subsequently exposed to an interaction station where the fluorescent/radioactive signal is detected (see pages 7-8, in particular the 1st full paragraph of page 8; see also claim 1).

Regarding claim 19, the system is a linear polymer analysis system (abstract).

Regarding claim 20, Tegenfeldt teaches that the system is useful for performing a sequencing application wherein a nucleic acid is labeled with a fluorescent or radioactive label and subsequently exposed to an interaction station where the fluorescent/radioactive signal is detected (see pages 7-8, in particular the 1st full paragraph of page 8; see also claim 1).

Regarding claims 22 and 23, the linear polymer analysis system of Tegenfeldt is useful for analyzing fluorescently labeled nucleic acids (pages 7-8 and claim 1).

Regarding claim 33, the system is capable of analyzing single polymers (page 8).

Regarding claim 34, the system described by Tegenfeldt is an optical mapping system (page 7, line 33 – page 8, line 4).

Regarding claim 68, Tegenfeldt teaches a method (see page 9, lines 6-15) comprising (a) generating optical radiation of a known wavelength to produce a localized radiation spot, (b) passing a polymer through a microchannel, (c) irradiating the polymer at the localized spot, (d) sequentially detecting radiation resulting from interaction of the polymer with the optical radiation at the localized radiation spot, and (e) analyzing the polymer based on the detected radiation.

Tegenfeldt teaches that the above method is useful for sequencing a nucleic acid molecule or expression mapping, stating, "Since generation of expression maps involve the sequencing and identification of cDNA or mRNA, more rapid sequencing necessarily means more rapid generation of multiple expression maps (page 2, lines 3-5)."

Tegenfeldt also states, "The methods disclosed herein provide much longer read lengths than achieved by the prior art and a million-fold faster sequence reading (page 11, lines 13-14)."

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to use the detection system of Tegenfeldt to analyze the hybridization patterns produced by the method of Taira. As noted above, Tegenfeldt expressly taught that the disclosed linear analysis system possessed several advantages compared to conventional detection methods, namely increased assay speed and the ability to analyze longer nucleic acid fragments

(see page 2, lines 3-5 and page 11, lines 13-14). Since the methods of Taira were directed to determining ribozyme binding sites and identifying the target nucleic acids associated with particular phenotypes, an ordinary artisan would have been motivated to analyze the binding reactions of Taira using the single molecule linear polymer analysis system of Tegenfeldt in order to obtain a rapid and efficient detection method. An ordinary artisan would have also been motivated to utilize the linear polymer analysis method of Tegenfeldt, because its ability to detect single molecules (see page 8) would have increased the sensitivity of the method of Taira. Since Tegenfeldt taught that the proposed read length is on the order of several hundred thousand nucleotides (see page 11), an ordinary artisan would have expected a reasonable level of success in analyzing the binding reactions of Taira using single molecule linear polymer analysis as taught by Tegenfeldt. Thus, the methods of claims 19, 20, 22, 23, 33, 34, and 68 are *prima facie* obvious over Taira in view of Tegenfeldt.

12. Claims 21-23 and 32 rejected under 35 U.S.C. 103(a) as being unpatentable over Taira et al. (US 2003/0199471 A1; newly cited) in view of Bertrand et al. (RNA (1997) 3: 75-88; newly cited).

Claim 21 is drawn to the method of claim 1, wherein the binding pattern is determined by fluorescence in situ hybridization (FISH). Claims 22 and 23 are drawn to the method of claim 13, wherein the nucleic acid tag molecule is labeled with a fluorescent molecule that is detected with a fluorescence detection system. Claim 32 is drawn to the method of claim 31, wherein the nucleic acid binding enzyme is directed indirectly using an antibody that specifically binds thereto.

Taira teaches the methods of claims 1, 2, 5, 6, 9, 11-16, 24-27, 31, 91, 125, 126, 128, and 130, as discussed above.

Taira does not teach determining the binding pattern using FISH as required by claim 21. Taira also does not teach labeling the nucleic acid tag molecule with a fluorescent molecule as required by claims 22 and 23. Taira also does not teach detecting the nucleic acid binding enzyme using an antibody that specifically binds thereto.

Bertrand teaches methods of controlling the intracellular localization of ribozymes (see abstract and page 76). Regarding claims 21-23, Bertrand teaches detecting the intracellular localization of the ribozymes using FISH (see Figure 5, pages 79-81, and page 87).

It would have been *prima facie* obvious to monitor the intracellular localization of the helicase-ribozyme conjugates of Taira using FISH. Since Taira taught using Northern blotting to monitor the intracellular localization of the ribozyme conjugates (paragraphs 58, 62, 122-124, 145-146, 161, and 177-178), an ordinary artisan would have been motivated to substitute any known method for monitoring the intracellular localization of ribozymes, such as the FISH method of Bertrand, recognizing that it was an art-recognized equivalent known to be useful for the same purpose. As noted in MPEP 2144.06, it is *prima facie* obvious to substitute art-recognized equivalents known to be useful for the same purpose in the absence of unexpected results. An ordinary artisan also would have recognized from the teachings of Bertrand that the disclosed FISH method was a faster and simpler method of determining the intracellular localization of the ribozyme-helicase conjugates, and therefore, would have been motivated to substitute this method for the Northern blotting method described by Taira. Furthermore, as noted in MPEP 2144.07, it is *prima facie* obvious to select a known material based on its

suitability for the intended purpose in the absence of unexpected results. In this case, Bertrand taught that the disclosed FISH method was suitable for determining the intracellular localizaation of ribozymes (see Figure 5, pages 79-81, and page 87). Therefore, an ordinary artisan would have been motivated to use this method to determine the intracellular localization of the ribozyme conjugates of Taira with a reasonable expectation of success. It is noted that determining the intracellular localization of the ribozyme conjugates of Taira using the FISH method of Bertrand would result in indirect labeling of the nucleic acid tag molecule (the ribozyme) with a fluorescent label and detection using a fluorescence detection system as required by claims 22 and 23. Finally, regarding claim 32, an ordinary artisan would have been motivated to perform the fluorescence in situ detection step using a fluorescently labeled binding partner specific for any component of the helicase-ribozyme conjugate of Taira (*e.g.* the helicase portion). An ordinary artisan would have had a reasonable expectation of success in detecting the helicase portion of the conjugates, since Taira taught antibodies that specifically bound to the helicase (paragraph 63). Thus, the methods of claims 21-23 and 32 are *prima facie* obvious over Taira in view of Bertrand.

Response to Arguments

13. Applicant's arguments filed on November 4, 2008 regarding the rejection of claims 1, 2, 5-7, 11, 14, 16, 24-26, 31, 91, 126, 128, and 129 are rejected under 35 U.S.C. 102(b) as being anticipated by Cheng have been fully considered, but they were not persuasive. Applicant argues that the reference does not teach all of the limitations of the claims as amended. In particular, Applicant argues that Cheng does not teach a first step of "providing a conjugate comprising a

nucleic acid tag molecule and a nucleic acid binding enzyme" followed by a second step of "contacting a nucleic acid polymer with the conjugate" as required by amended claims 1, 91, 126, and 129 (see pages 9-10). This argument was not persuasive, because the claims as written do not exclude a method wherein the "providing" step and the "contacting" steps occur simultaneously. As discussed above, in the method of Cheng, the providing and contacting step occur simultaneously upon UV irradiation of mixture comprising the reverse transcriptase, dT_{10} primer, and rA_{12-18} template. See also MPEP 2111.01 II, which states that it is improper to read a particular order into a series of process steps when a particular order is not required or implied as a matter of logic or grammar. Since Applicant's arguments were not persuasive, the rejection has been maintained.

Applicant's arguments filed on November 4, 2008, regarding the rejection of claim 125 under 35 U.S.C. 102(b) as being anticipated by Fisher, have been fully considered, but they were not persuasive. As an initial matter, it is noted that the previously cited Fisher patent has been replaced with the earlier-published WIPO document. Since the disclosures of both the previously cited patent and the presently cited WIPO document are the same, Applicant's arguments filed on November 4, 2008 remain pertinent to the new grounds of rejection. Applicant argues that Fisher does not teach all of the limitations of amended claim 125, specifically the requirement for the nucleic acid binding agent to non-specifically bind to the nucleic acid polymer (see page 10). This argument was not persuasive, because as discussed above, the nucleic acid binding agent (P1 nuclease) inherently binds non-specifically to the nucleic acid polymer at least transiently, since it is conjugated to a short oligonucleotide that

specifically binds to the nucleic acid polymer. It is also noted that there is no requirement for an inherent feature to be recognized at the time of invention (MPEP 2112).

Applicant's arguments, see page 11, last paragraph – page 12, first paragraph, filed on November 4, 2008, with respect to the rejection of claims 1, 2, 5-7, 9, 11-13, 16, 17, 22-31, 91, 126, and 128-130 under 35 U.S.C. 103(a) as being unpatentable over Fisher as evidenced by Chaudhry in view of Kigawa have been fully considered and are persuasive. This rejection has been withdrawn. In view of the arguments presented at page 11, last paragraph – page 12, first paragraph the rejection of claims 1, 2, 5-7, 9, 11-13, 16, 17, 22-31, 91, 126, and 128-130 under 35 U.S.C. 103(a) as being unpatentable over Fisher as evidenced by Chaudhry in view of Rye and further in view of Thompson has also been withdrawn.

Applicant's arguments, see pages 14-16, filed on November 4, 2008, regarding the rejections of claims 19, 20, 32-34, and 68 made under 35 U.S.C. 103(a) citing Fisher as evidenced by Cauchy in view of Kigawa as the primary combination of references have been fully considered and are persuasive. These rejections have been withdrawn.

Conclusion

14. No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on Monday – Friday, 7:30 – 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Kenneth R Horlick/
Primary Examiner, Art Unit 1637

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